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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/961,128	09/21/2001	Marianne Kearney	49138 (71417)	4197

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EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 01/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/961,128	KEARNEY ET AL.	
	Examiner	Art Unit	
	Celine X. Qian Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-12 and 15-25* is/are pending in the application.

4a) Of the above claim(s) *18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-12,15-17 and 20-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/29/03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1205*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-3, 6-12, 15-25 are pending in the application. Claims 18 and 19 are withdrawn from consideration for being directed to non-elected subject matter.

This Office Action is in response to the Amendment filed on 12/15/05.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/15/05 has been entered.

Response to Amendment

The rejection of claims 1-3, 6-12, 15-17 and 20-25 under 35 U.S.C. 103 (a) is maintained for reasons set forth of the record mailed on 12/28/04 and further discussed below.

Election/Restrictions

Applicants request the reconsideration of the restriction requirement and rejoin claims 18 and 19 with originally elected Group II. Applicants assert the search and examination of claims 18 and 19 would overlap the claims of 1-3, 6-12 and 15-17.

Applicants' argument has been considered but deemed unpersuasive. As discussed in the previous office action, claims 18 and 19 are drawn to a method of preparing a plasmid producing biologically active endothelial cell mitogen protein. It is a different invention from the originally elected invention (group II), which is directed to a method for testing a plasmid containing a gene encoding for an endothelial cell mitogen for the ability to produce a biologically active

mitogen protein. Each method comprises different steps which does not render obvious of each other. A search of the invention of Group II is not co-extensive with the search of claims 18 and 19, thus is burdensome. Since Applicants have not distinctly and specifically point out the supposed error, the requirement is still deemed proper and is therefore made FINAL.

Response to Arguments

Claim Rejections – 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-3, 6-12 and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sugihara et al., in view of Buttke et al. and Breier et al.

In response to this rejection, Applicants provided a declaration by Dr. Kearney and argue that there is a quantitative difference between the conditional medium produced by stable transfection and transient transfection, wherein a transiently transfected culture would be expected to yield less protein than a culture stably transfected with the same plasmid. Applicants assert that the instant invention utilizes analysis of cell viability as a tool to confirm sufficient protein production by the gene construct because the proposed gene product is known to act as a survival factor for specific cell types, thus is an improvement over the art. Applicants argue that Sugihara describes a cell mitogenic assay using incorporation of ^{3}H-thymidine during the cell cycle as a means of measuring cell proliferation whereas the instant invention provides for a method for testing the survival of cells as measured by a cell viability assay. Applicants argue that these traits are quite different because viable cell are not necessarily undergo mitosis. Applicants further argue that Buttke repeatedly distinguishes between the use of the ^{3}H-

thymidine assay to measure cell proliferation and the use of the MTS/formazan assay to measure cell viability. Furthermore, Applicants argue that the cell proliferation assay of Sugihara and cell viability assay of Buttke are measuring two different parameters, and Buttke cannot supply the deficiencies of Sugihara. Applicants assert that there is no motivation for one of skill in the art to use stable transfection technique and cell proliferation assay of Sugihara to perform the transient transfection and cell viability assay of the present invention. Applicant assert that there is no suggestion in Buttke that measurement of cell proliferation would be interchangeable with measurement of cell viability, such that Buttke teaches away from Sugihara by emphasizing a marked preference for the need for both tests. Moreover, Applicants argue that Breier cannot supply the deficiencies of Buttke and Sugihara because Breier does not teach measuring cell survival. Applicants further assert that Buttke teaches away from Breier by emphasizing a marked preference for the need for measuring and comparing two different cell parameters. Finally, Applicants assert that there is no motivation in Breier to combine the teaching of Sugihara and Buttke. Applicants thus conclude that the claimed invention is not obvious in view of the cited prior art.

These arguments have been fully considered but deemed unpersuasive. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The instant rejection is based on the above analysis. It is unclear the production of more or less protein in the medium by either stable or transient transfection would affect the above analysis. If the Applicants consider such method yielded unexpected results, such results are nowhere recited in the claim. In fact, based on Applicant's own assertion that VEGF is known as a survival factor for certain cell type (HUVAC) renders the invention obvious because one of ordinary skill in the art would thus pick an assay such as MTS to measure cell survival. The examiner understands that a MTS assay measures cell viability and thymidine incorporation assay measures cell proliferation. While they are two different parameters, the proliferation assay in fact indirectly reflects cell survival because a non-viable cell cannot proliferate. Further, one ordinary skilled in the art would recognize that measuring one parameter does not excludes one from the measuring other parameter(s) especially based on the teaching of Buttke. Buttke provides sufficient reasons for combining the teaching because it teaches that it is of particular interest to compare MTS production with thymidine uptake in cell culture. This teaching is indeed a motivation to combine the reference because of the difference between two assays. As such, one of ordinary skilled in the art has sufficient reason to combined the teaching of Sugihara and Buttke and reach the present invention of testing the mitogenic activity of the endothelial cell mitogen encoded by a test plasmid and measure endothelial cell viability when such cells are cultured with the conditioned media that comprises said mitogen. Breier et al. simply teach that Cos-1 cells are capable of being used to express VEGF, an endothelial cell mitogen. It does not have to provide teaching to remedy the alleged deficiency of Sugihara or Buttke for not providing a motivation to combine the references. Buttke neither teaches away from Sugihara nor Breier because it provides sufficient motivation to combine the teaching of the references.

Therefore, the claimed invention is obvious in view of the combined teaching of Sugihara, Buttke and Breier.

The newly added claims 20, 21, 23 and 24 are rejected for same reasons as set forth of the record mailed on 12/28/04 and discussed above. In claims 20 and 23, the added step of determining the ability of the test plasmid to produce biologically active endothelial mitogen protein is a mere repetition of the preamble, it does not set forth any parameter for such determination. In claims 21 and 24, the added step recites the intended use for the endothelial mitogen protein. However, the specification fails to teach how to determine such protein is optimal to use in human gene therapy other than measuring cell survival as recited in steps a) through d) (claim 1) or f) (claim 10). Therefore, it is not a further limitation to the parent claim. Thus, the combined teaching of the cited references still renders the invention obvious for same reason discussed previously.

New Grounds of Rejection Necessitated by Applicant's Amendment

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 22 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sugihara et al., Buttke et al., and Hu et al (US 5,932,540).

The teaching of Sugihara et al. and Buttke et al. were discussed in the previous office actions. However, neither reference teaches a plasmid contains a gene encoding for VEGF2.

Hu et al. teach polynucleotides and polypeptides encode VEGF2 (see examples 1-3). Hu et al. further teach endothelial mitogen assay using HUVEC cells to measure VEGF2 biological activity.

It would have been obvious to one of ordinary skill in the art to measure biological activity of VEGF2 by using the claimed method based on the combined teaching of Sugihara et al., Buttke et al., and Hu et al (US 5,932,540). The obviousness of using MTS to measure cell survival treated with conditional media comprising VEGF is discussed in the previous office action. Since VEGF 2 is a isoform of VEGF and the sequence is disclosed by Hu et al., one of ordinary skill in the art would have reasonable expectation of success to test its biological activity by measuring cell survival of HUVEC cells as claimed. Therefore, the claimed invention is *prima facie* obvious at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X. Qian Ph.D. whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine X Qian Ph.D.
Examiner
Art Unit 1636

CELIAN QIAN
PATENT EXAMINER